STUDY OF CARDIAC DYSFUNCTION AMONG THE CHILDREN LIVING WITH HIV /AIDS IN THE AGE GROUP OF 2-12 YEARS IN AN URBAN REFERRAL CENTRE

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CERTIFICATE

Certified that this dissertation entitled "STUDY OF CARDIAC DYSFUNCTION AMONG THE CHILDREN LIVING WITH HIV /AIDS IN THE AGE GROUP OF 2-12 YEARS IN AN URBAN REFERRAL CENTRE" **is a bonafide work done by** Dr.M.ANITHA, M.D., **Postgraduate student of Paediatrics , Institute of Child Health and Hospital for Children, Egmore, Chennai –8, attached to Madras Medical College, during the academic year 2006-2009.**

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CONTENTS

INTRODUCTION

In India HIV/AIDS epidemic is now 22 years old. Within this short period it has emerged as one of the most serious public health problem in the country. Nearly six million people are estimated to be living with HIV/AIDS in south east Asia and CLHA less than 15yrs of age are estimated to be 1,20,000 compared to North America of 11,000.[44] This pandemic has caused the death of over 17,000 in 2007[44] Over 6,800 people are diagnosed positive for HIV a day, out of which 1200 are in children less than 15yrs of age globally.[44] The prevalence in children less than 15yrs of age is 3.8 % in India. Tamilnadu is considered as one of the high burden states in India, holding 10 % of the national PLHA.[44]

There are 2 types of HIV Virus, HIV –1 & HIV-2. The type common in the Indian Sub-continent is HIV -1 with major group M, sub group C whereas, sub group B is common in USA. Perinatal transmission accounts for the most common mode of transmission in children. Other modes of transmission include breastfeeding and blood transfusion.[25]

The currently available antiretroviral (ARV) drugs and treatment of opportunistic infection have converted HIV infection into a chronic illness.[34] The HIV disease may affect all body systems, including the cardiovascular system.[34]Since ARV drugs do not eliminate the HIV virus from the body, their use may simply postpone the development of heart disease, yet some of those drugs like zidovudine are cardiotoxic themselves and have been associated with heart disease.[33,35]

As pulmonary diseases in HIV infection are more effectively prevented and treated, the proportional morbidity and mortality of heart disease among children with HIV/AIDS has increased.[5,37] Most of the published studies about heart disease in HIV/AIDS have been done in adults and abroad.[6-9,36]

The few published studies of heart disease among HIV infected children in India, have used a small sample size (<50) [7] or were highly selective (including only children with symptomatic HIV disease or those who were very sick.) In many clinical situations, HIV infected children are not routinely evaluated by echocardiography.

Previous studies have shown that heart diseases in HIV/AIDS patients are usually sub-clinical, but may be severe.[8,4] When the signs and symptoms of cardiac dysfunction are present, they are non-specific and are often attributed to non-cardiac pathologies especially pulmonary disease.[23,39]

From the beginning of the HIV epidemic in the developed world it was recognized that the heart could be involved, but that significant clinical involvement of the heart was unusual. On further review of autopsy series and clinical series and especially with the study of patients with AIDS who had echocardiography, it was apparent that abnormalities of the heart were seen frequently, even though symptomatic heart disease still remained unusual.[11]

According to the western literature, cardiac abnormalities develop at a high frequency in chronically HIV infected individuals irrespective of the antiretroviral

therapy,[12,40] a fact which has been recognized, since the early years of the epidemic. The spectrum and epidemiology of cardiac disease in HIV infection have been extensively reviewed with the development of ventricular dysfunction and dilated cardiomyopathy being of particular clinical significance and occurring among HIV infected people at much higher rates than among HIV negative individuals[45, 46,52]. Prevalence of cardiac diseases among the CLHA in Sub Saharan Africa has been documented to be high.[5,20] The prevalence in the Indian sub continent has neither been estimated nor its impact on the survival.

Both infection with HIV and treatment of HIV infection with antiretroviral drugs[47] may affect the function of the heart and the vasculature. Direct infection of target tissues with HIV, inflammation and immunosuppression secondary to HIV infection and common co-morbid conditios like malnutrition, may all contribute to impairment of cardiac function.[47]

Therefore the present study was undertaken to study the prevalence of cardiac disease and its clinical profile in HIV infected children.

Etiopathogenesis

Pathogenesis of cardiomyopathy in HIV infection is poorly understood and it is likely to involve a combination of host, viral and environmental factors.

Possible etiology:

Infections	HIV, Toxoplasma gondii, Coxsackie virus group B, Epstein Barr virus, Adeno, cytomegalo virus
Cytokine mediated	TNF- α, Nitric oxide, TGF -β, Endothelin-1
Auto immunity	Anti cardiac myosin, Anti cardiac C protein
Drug related	Zidovudine,Interferon,foscarnet, doxorubicin,IL-2, amphotericin B, cocaine
Nutritional deficiency	Selenium, Vitamin B12, carnitine
Autonomic dysregulation	Cardiovascular sympathovagal dysfunction
Metabolic/Endocrine.	Anemia, Thyroid hormone related, Growth hormone related, Adrenal insufficiency, Hyperinsulinemia.
Associations	Encephalopathy, immunodeficiency (CD4 <100), length of suppression, HIV viral load

Pathogenesis

Infection

Myocarditis is the best-studied cause of dilated cardiomyopathy in HIV disease.[48] HIV infects myocytes but is not abundant (1 in > 2000 cells) or highly multiplicative in these cells. Despite the paucity of evidence of direct myocyte involvement, the HIV infection clearly causes structural and functional injury to the heart as a whole. Myocarditis in HIV infection is mostly of unknown etiology, with many studies identifying an underlying pathology in only minority of cases, though cytomegalo virus, adeno virus,Cox sackie virus B3, Epstein Barr virus, Toxoplasma gondii,

Mycobacterium avium complex, Candida spp, Crytococcus neoformans, Coccidiodis imitis, Histoplasma capsulatum, Aspergillus species and Pneumocystis jiroveci have all been documented.[10,35]

In evaluating whether HIV itself may play a direct role in induction of local myocardial inflammatory response, contractile dysfunction, or pathologic remodeling, multiple investigators have detected HIV viral genome and/or viral proteins in the hearts of HIV infected people.[10,51]

HIV virion infects myocardial cells in patchy distributions, without a clear direct association between HIV and cardiac myocyte dysfunction.[48] How the virus enters CD 4 receptor negative cells, such as myocytes is unknown. Non myocyte populations comprise of up to 70% of the total cellular constituency of the myocardium and consist of a mixed assemblage of cell types, including substantial populations of dendritic cells and macrophages, which can serve directly as targets of HIV infection. This environment represents a volatile setting in the context of HIV infections.[10]

Investigators using methods with a high degree of morphologic discrimination at the tissue level have in almost all cases found productive HIV infection to be restricted to cells within the myocardial interstitium, [50] most consistent with macrophages and T cells, such that previous long standing controversy over the potential for HIV to directly infect cardiomyocyte has largely been resolved. The virus persists in reservoir cells eg.dendritic cells, in the cerebral cortex and in macrophages that may be present

between myocardial cells, even after effective ART.[48]

Reservoir cells and associated cytokine signaling may be important in the development and progression of cardiomyopathy and encephalopathy. Reservoir cells, e.g. dendritic cells, may play a pathogenetic role in the interaction between HIV and the myocyte and in the activation of multifunctional cytokines eg. Tumor necrosis factor (TNF-α), Interleukins (1L-1, IL-6, IL-10) that contribute to progressive and late tissue damages.[48]

Another potential mechanism causing tissue damage results from lymphocytic myocarditis, an inflammatory process which has been documented at high frequencies in HIV infected people at later stage of disease progression and which constitutes one of several conditions known to predispose to development of DCM irrespective of HIV infection status.[50] The inflammatory infiltrates in HIV associated myocarditis are consistently documented to mainly comprise of CD-8 receptor positive T cells with variable number of macrophages and a paucity of CD-4 cells which may reflect the decreased CD-4: CD-8 ratio seen in HIV positive patients. The prevalence of lymphocytic infiltration into the myocardium is as high as 52%.[10,35]

Cytokine mediated

Important potential contributor to development of HIV cardiomyopathy is proinflammatory cytokine excess resulting from effects of HIV associated cytokine

dysregulation. The most important cytokine is TNF – α. The local myocardial tissue environment has been demonstrated to be a rich potential source of inflammatory cytokines, with both cardiomyocytes and locally resident non-myocytic interstitial cell populations competent to produce a variety of inflammatory mediators, and heart tissue capable of generating as much or more of TNF-α per gram of tissue in response to endotoxin stimulation as liver or spleen.[50]

Other cytokines implicated in the pathogenesis of HIV cardiac disease include IL-1, IL-2, IL-6, IF -δ,IL-1 and TNF can increase nitric oxide concentrations, which in turn can modulate inotropic response to catecholamines. IL-2 and IL-6 also have a negative inotropic effect on the heart, mediated by an increase in nitrous oxide production.[50]

The mechanisms by which the inflammatory cytokines generate their effects in the myocardium have been studied. Cytokine induced products of the sphingomyelinase pathways, nitric oxide generated by inducible nitric oxide systhetase (iNOS), and reduced cyclic AMP response to β-adrenergic stimulation and all appear to act as mediators of cardio depressant effects.

On a molecular level, these effect result from modulation of intra-cellular calcium transport, antagonism of cyclic AMP-mediated protein kinase A effects, alteration of sensitivity of myofilaments to calcium binding, S-nitrosylation of thiol residues on contractile proteins, functional uncoupling of - β adrenergic receptor stimulation from

adenyl cyclase activity and possibly alteration of β -adreno receptor internalization kinetics. [50]

Inflammatory cytokine-induced pathologic remodeling yields.

* Chamber dilatation

* Myocardial hypertrophy

* Fibrosis attributable to dysregulation of matrix metallo proteinases (MMP), tissue inhibitor of metallo proteinases (TIMP) balances, increased expression of TGF- β

* Alteration in susceptibility to cardiomyocyte apoptosis

* Stimulation of hypertrophy and foetal gene expression patterns

Auto immunity

Cardiac specific auto antibodies (anti α myosin auto antibodies) have been reported in up to 30 % of patients in HIV associated cardiomyopathy. Apparent improvement of left ventricular function in children with AIDS using intravenously administered immunoglobulin is also suggestive of an immunologic etiology for the left ventricular dysfunction.[13]

Malnutrition

Nutritional causes for HIV related cardiac disease include selenium deficiency, L-

carnitine deficiency and overall malnutrition..[10,52,53]. Levels of vitamin B12, growth hormone and thyroid hormone may also be altered in HIV disease and all have been associated with left ventricular dysfunctions.[10,12]

Wasting syndrome and weight loss are common in HIV positive patients, characterized by loss of lean body mass, especially muscle protein. In the absence of HIV infection, malnutrition has been linked to decrease in LV mass, LV volume, ventricular function and blood pressure.[30] It is possible that inadequate nutrition may have contributed to the sub normal hypertrophic responses relative to LV dimension observed in these patients. Nevertheless, wasting is predictive of overall mortality and cardiac mortality in children with HIV. Severe anemia may also be a cause of as well as worsen the effect of cardiac disease in HIV positive patients.

Drug toxicity:

The cardiovascular complications of commonly used pharmacotherapeutic agents in pediatric HIV infection [10]

Zidovudine	Cardiac myocyte toxicity(diffuse destruction of cardiac mitochondrial ultra structures and inhibition of mitochondrial DNA replication). hypersensitivity reaction
Pentamidine	Prolonged QTc/ Torasade, cardiac arrest/anaphylaxis, Hypotension, tachycardia
Trimethoprim sulphamethoxazole	Prolonged QTc/ Torasade, cardiac arrest/ anaphylaxis, hyperkalemia.
Ganciclovir	Ventricular tachycardia
Foscarnet	Reversible severe cardiac failure, renal insufficiency, Electrolyte abnormalities.
Systemic corticosteroids	Ventricular hypertrophy/dysfunction.
Growth hormone	Activation of rennin-angiotension system. Ventricular hypertrophy/dysfunction
Interlerleukin-2	Myocardial depression, myocarditis,infarction, arrythmias
Interferons:	SVT, cardiomyopathy, coronaryartery decreased perfusion / hypotension.

Mechanism by which HIV infection may adversely affect the vasculature

- Endothelial dysfunction.
- Lipid disorders associated with HIV infection.
- Viral protein related endothelial cell activation.
- Systemic inflammatory cytokine - chemokine dysregulation.
- Direct HIV infection of endothelium & vascular smooth muscle cells.
- Enhanced atheroma formation by activated macrophages.
- Prothrombotic state

Foetal and congenital effects of HIV infections

Evidence that either direct infection with HIV or developing in an HIV infected milieu could be related to foetal cardiac abnormalities, has been presented. *Vogel et al[24] studied 175 children who had perinatally acquired HIV antibodies from their mothers. Five children had CHD including ASD,TOF,TA,VSD with PS. The prevalence of 2.8% was significantly higher than the 0.8 % seen in the general population.[25] Recent abstracts of P^2C^2 longitudinal study found a high prevalence of congenital cardiovascular malformation in children born to mothers who were HIV positive.[49] Foetal development in a mother infected with the HIV with the concomitant increase in cytokine &

nutritional deficiencies, other physiologic effects of maternal HIV infection, may also affect heart functions after birth, regardless of the HIV status of the child.

Cardiovascular manifestations of HIV disease

Recent studies have shown cardiac involvement in as, many as 45% to 65% [6-10]of people infected with human immuno deficiency virus (HIV).

Before the introduction of HAART the most common cardiac manifestations were dilated cardiomyopathy, endocarditis, myocarditis, pericarditis, right ventricular failure caused by pulmonary hypertension and conduction system involvement. However, recent reports of myocardial infarction in young HIV infected patients on HAART have raised concerns about premature coronary artery disease.[47]

Dilated cardiomyopathy

HIV disease is an important cause of dilated cardiomyopathy, with a prevalence reported of 3.6% among the CLHA. Patients with HIV infection and DCM can have a much worse prognosis than those with DCM alone, hazard ratio of death 4.0.[12]

Pathological mechanism

There are several possible mechanisms for the increased LV dimension and mass in pediatric HIV Infection, including HIV effect, after load excess, and anemia/malnutrition, none of which fully accounts for the marked dilatation and

hypertrophy that have been documented. HIV infection may directly or indirectly affect the cells of the pediatric heart.

Pericardial effusion

Pericardial effusion appears to be less prevalent in children than in adults. In children with vertically transmitted HIV infection, pericardial effusion tends to occur less frequently and is small and progressive. Studies have documented a 16 % to 26% prevalence of pericardial effusion in HIV positive children. [22,31] 69% of these children with effusion had associated cardiac abnormalities (ventricular dilatation or hypertrophy, myocarditis or pericarditis). Thus the relatively high prevalence of pericardial effusion reported in children may reflect upon children with more advanced disease.

Pericardial effusion in HIV disease may be related to opportunitic infection, but most often a clear etiology is not found. Miscellaneous causes are capillary leak,wasting,malnutrition,hypothyroidism,prolonged acquired immunodeficiency.

The effusion may be a part of a generalized serous effusion process also involving pleural and peritoneal surfaces. The effect of HAART therapy in pericardial effusion is still largely unexplored.[56]

Endocarditis

Few cases of endocarditis have been reported in children. [55] Right-sided valves are

predominantly affected and the most frequent agents are staphylococcus aureus (>75%of cases), streptococcus pnemoniae, haemophilus influenzae, candida Albicans, Aspergillus fumigatus and cryptococcus neoformans.[56] Non-bacterial thrombotic endocarditis also known as marantic endocarditis , occcurs in 3% to 5% of AIDS patients mostly in the patients with HIV wasting syndromes.[11]

Effect of HIV on the vasculature

HIV can damage endothelium through several mechanisms. Tat protein, a small cationic polypeptide that can be released from infected cells, interact with at least 3 different types of receptors present on the surface of endothelial cells. The resultant activation of several signal transduction pathways triggers the expression of adhesion molecules, vascular endothelial growth factors and platelet activating factors. As a consequence, Tat protein causes endothelial dysfunction. [56]

Pulmonary hypertension:

The incidence of HIV-associated pulmonary hypertension is estimated to be 1/200, much higher than the 1/200000 found in the general population. Pulmonary hypertension has been documented in adults and children, often as a consequence of LV dysfunction, repeated respiratory infections, or thrombo-embolic disease, but occasionally as a primary process with no discernible cause. The incidence of pulmonary hypertension has been estimated to be 0.5% in hospitalized patients with

AIDS.[10]

Therapy includes anticoagulation & pulmonary vasodilatation with Epoprostenol and Endothelin antagonist. Effects of HAART regimens on the clinical course of HIV associated pulmonary hypertension are unknown. The prognosis is poor with survival of 6 months despite ART.

Autonomic Dysfunction:

HIV infection has been associated with a wide spectrum of central and peripheral nervous system disorders, including autonomic dysfunction and neuropathy, which may occur in patients at any stage of the infection and have significant effect on cardiovascular reflexes. The hemodynamic abnormalities, dysrhythmias, unexplained arrest and sudden death are common in the children infected with HIV especially when acute deterioration, intervention or neurologic involvement (encephalopathy) is present. The pathogenesis is unclear, could be directly associated with CNS effects, or vasculitis affecting peripheral nerves leading to depression of responses.

Clinical spectrum of cardiac abnormalities:

- Chamber dilatation & hypertrophy
- Ventricular dysfunction
- Congestive heart failure
- Pericardial effusion.

- Pulmonary hypertension.
- Congestive heart failure.
- Cardiac arrhythmias /arrest.

Diagnosis of HIV associated cardiac disease

Physical examination: -

The symptoms of fever, dyspnoea, tachypnoea, and tachycardia are commonly attributed to pulmonary process even when the primary pathology is cardiac. The cardiac manifestations are mostly sub clinical and the findings on examination may not correlate with clinical severity.[10,6]

Chest Radiography: -

Cardiomegaly or pulmonary congestion may be evident on chest radiographs. The chest x ray may often show no cardiomegaly despite ECHO proven disease.[11]

Electrocardiography:

ECG abnormalities are common. The spectrum of ECG abnormalities seen in children who are HIV positive are tachycardia (49%-70%), ventricular hypertrophy (20% - 30%). Other findings include ST segment and T wave changes (7%-33%) and rhythm disturbances including marked since arrhythmia, atrial ectopy, and ventricular arrhythmia. 24 hours Holter monitoring is useful with history of syncope or

hemodynamic abnormalities.

Echocardiography:

Echo has been the best non- invasive tool to accurately estimate the cardiac dysfunction in the HIV infected patients. It is also useful for follow up. By Echo we estimate the LV fractional shortening and the ejection fraction. In the echocardiography LV dysfunction, hypertrophy or dilatations are the common abnormalities. The prevalence of echo abnormalities varies from 15 to 60 %.[1-12] It picked up dilated cardiomyopathy (5%), pericardial effusion (10 %), pulmonary hypertension, RV dysfunction, hypertrophy and cor pulmonale. Vascular regurgitations can also be found.Ejection fraction and fractional shortening are taken as indices of left ventricular systolic function

Endomyocardial biopsy:

Myocarditis is often patchy and so it needs multiple samples.It may significantly affect treatment. Viral PCR is potentially useful.[10]

Cardiac Troponin: Troponin is a sensitive and specific marker of myocardial injury, and the performance of troponin assay is helpful in a risk benefit discussion about endomyocardial biopsy and in deciding the utility of intravenous immunoglobulin therapy in a particular patient.[47]

Brain Natriuretic peptide (N-terminal pro B type Natriuretic Peptide): It has shown to be very sensitive marker for symptomatic and asymptomatic cardiac dysfunction, prognosis, severity of the disease and response to therapy. Studies performing screening of children with HIV for cardiac disease by BNP have started in the west.[45]

Cardiac Isoform of Alpha 2 macroglobulin: Cardiac isoform of Alpha 2 macroglobulin, (CA2M)is a high molecular mass (182000mμ) , serum protein which is involved in the development of cardiac hypertrophy. Studies have confirmed that CA2M could be used as early a diagnostic marker for cardiac disease.[38]

Management

- The treatment for the heart failure and hypertension are similar to those in non-HIV infected children.

- Treatment of certain opportunistic infections with appropriate conventional antibiotic improves LV dysfunction. E.g.TB percarditis, cryptococcal, salmonella.

- Administration of HAART has shown improvement in the cardiac function. Studies have shown that there is statistical difference between the groups with and without triple combination treatment as regards the presence of LV dysfunction.[1]

Some children with heart disease and congestive heart failure who are unresponsive to anticongestive therapy improve with intravenous immunoglobulin

therapy.[13]

Monthly infusions of Intravenous Immunoglobulin to HIV infected children appear to be associated with more normal LV structure and function compared with untreated infected children. The Meta analysis showed a significant increase in wall thickness and reduction in peak wall stress with IVIG and with elevated IgG levels.[13]

Prognosis

Factors such as recurrent bacterial infections, wasting, encephalopathy, male gender, low CD 4 and IgG levels, and an earlier age at AIDS diagnosis may identify high risk patients.

Cardiac manifestations of HIV infected children are protean and common. The ability to identify patients particularly at high risk for cardiovascular abnormalities would improve cure because care of HIV infected children relies on accurate diagnosis and prompt management of underlying illness, including symptomatic cardiac diseases.

REVIEW OF LITERATURE

1. Ira Shah et al[7] in 2003 at Mumbai prospectively evaluated 26 children in the age group 1 to 9 years with perinatally acquired HIV for subclinical cardiac abnormalities during a period of six months. The study had excluded all children presenting with signs and symptoms suggestive of cardiac pathology and evaluated the asymptomatic children by echocardiography. Of the 26 children, 20 children (76.9%) demonstrated abnormal echocardiographic findings.18 children (69.2%) in category B (symptomatic HIV) had stastically significant abnormal echocardiographic findings ($p<0.02$). The commonest echocardiographic abnormalities seen were left ventricular dilatation in 38.5% and left ventricular hypertrophy in 38.5% children. In children with repeated lung infections pericardial effusion was demonstated in 3 children (11.5%). Mild tricuspid regurgitation was present in 3 cases. The relationship of cardiac abnormalities to the stage of HIV infections remained obscure.

He concluded that echocardiographic abnormalities were present even in HIV infected children who were asymptomatic for cardiac symptoms. The study recommended an annual echocardiographic evaluation to assess the progression of cardiac disease.

2. Sulaiman Lubega et al[3] in 2005 at Uganda recruited 230 HIV infected children in a cross sectional study and evaluated clinically and investigated them by electrocardiography and echocardiography following the criteria of the American

society of echocardiography. Heart abnormalities were detected in 51% of the children (40% by echocardiography alone and 26.5% by electrocardiography alone). Heart abnormalities were most prevalent in children with AIDS (76.2%) and least prevalent in children with asymptomatic HIV disease (25%). The abnormalities included were sinus tachycardia (21%), left ventricular systolic dysfunction (17%), right ventricular dilatation (14%), congenital heart disease (48%), dilated cardiomyopathy (3%), pericarditis (2.2%) and cor pulmonale (1.3%).

3. Pong port Y et al[6] studied the cardiac manifestations in HIV infected Thai children. He retrospectively reviewed the medical records of 27 infants infected with HIV perinatally, who presented with cardio vascular problems at a tertiary care hospital between 1995 and 2000. The mean age and initial cardiac evaluation was 36 months (range 8-65). Signs and symptoms included dyspnoea in all cases, edema in 12 (44%), finger clubbing in 11 (41%), cyanosis in 6 (22%) and S3 gallop in 8 (30%). Echocardiographic abnormalities included pericardial effusion in 12(44%), right ventricular dilatation in 12 (44%), pulmonary hypertension in 11(41%), diminished left ventricular fractional shortening in 10 (37%), left ventricular dilatation in 9 (33%) and combined ventricular dilatation in 2 (7%) cases. Left ventricular dysfunction did not correlate with HIV CDC classification, age, nutritional status or clinical signs and symptoms.

4. Lipshultz SE et al[9] in (P^2C^2) 1998 studied 196 vertically HIV infected children

with a baseline echocardiogram and 2 years follow up every 4 months. Although 88% had symptomatic HIV infection only 2 had congestive heart failure at enrollment, with a 2 year cumulative incidence of 4.7%. All mean cardiac measurements were abnormal at baseline (decreased left ventricular fractional shortening and contractility and increased heart rate and LV dimension, mass and wall stresses). Most of the abnormal baseline cardiac measurements correlated with depressed CD4 cell count Z scores and the presence of HIV encephalopathy. The study concluded that sub-clinical cardiac abnormalities are common, persistent and often progressive. Depressed LV function correlated with immune dysfunction at baseline but not longitudinally, suggesting that CD4 cell count may not be a useful surrogate marker of HIV associated LV dysfunction and development of encephalopathy signals a decline in fractional shortening.

5. The Prospective Pediatric and Cardiac Complications (P^2C^2) HIV multicentre study conducted by Starc et al[8] in 1999 , where 205 HIV vertically infected children were enrolled at median age of 22 months. Most of the children had symptomatic HIV infection (89%) at enrollment. Children underwent cardiac evaluation including 2D echo, Doppler studies of cardiac function, 15 lead surface ECG, 24 hrs ambulatory ECG monitoring and a chest radiograph. The children who had cardiac impairment which was defined as having either LV fractional shortening <25% after 6 months of age, CHF or treatment with cardiac medications was 5.7%. The prevalence of echocardiographic LV enlargement (LV end diastolic dimension Z score >2) at the time of first echo was 8.3%. There were 14 prevalent cases of cardiac impairment. The study concluded that in

addition to sub clinical abnormalities an important number of HIV infected children develop clinical heart disease. The study recommended clinicians to maintain a high degree of suspicion for heart disease in HIV infected children and that all HIV infected infants and children should have a thorough base line cardiac evaluation.

6.Maria Surely Bezerra Diogenes et al[2] conducted a cardiac longitudinal study of children perinatally exposed to HIV type 1 from July 1996 to July 2004.The objective was to determine the frequency of cardiac abnormalities and its natural history history in perinatally infected children. The study concluded that electrocardiographic changes were significantly more frequent than clinical and echo findings. This study also said that higher prevalence of abnormalities was found among children belonging to the most advanced clinical and immunological category.

7. Maria do Carno et al[1] between 1999 and 2002 in Brazil conducted a cross sectional study with a cohort after18±6 months of AIDS diagnosis. The study included a total of 93 children with a confirmed diagnosis of AIDS with vertical transmission, with no malignancies and who underwent echo. Cardiac abnormalities were assessed in patients who were not treated (G1) and patients who were treated (G2) with combination anti retroviral therapy. Cardiac involvement was present in 40 children (43%). The presence of left ventricular dysfunction (G 1: 39.10%; G 2: 10.60%) and the isolated enlargement of the left ventricle (G 1: 6.60%; G 2: 14.90%) were the most frequent findings. A significant association between the groups without and with combination

antiretroviral therapy as regards the presence of left ventricular dysfunction PR= 3.42 ; (1.41-8.26); p =0.02 and malnutrition PR= 1.79 ;(1 – 3.20); p = 0.04 was observed.

8. Plein et al[58] in 1999 studied the prevalence of cardiac abnormalities in a Pediatric population with HIV. About 22 children had cardiac evaluation by echo. Cardiac lesions were found in 18% consisting of pericardial effusion in 3 children, wall motion abnormalities in 3 children and acute aortic endocarditis in one child. All cardiac abnormalities were staged as per CDC classification

STUDY JUSTIFICATION

Children infected with HIV may develop a wide range of cardiovascular abnormalities, some of which are to be associated with poor survival. The baseline echocardiographic abnormalities are common, persistent and often progressive. In many clinical situations, HIV infected children are not routinely evaluated by Echo. When the signs and symptoms of cardiac dysfunction are present, they are non specific and are often attributed to non cardiac pathologies especially pulmonary diseases.

Most of the published studies about heart disease in HIV / AIDS have been done in adults. Evidence from adult studies cannot be easily be extrapolated to children because the epidemiologic correlates of adult high risk group may not apply to children. Adult studies are also confounded by traditional cardiac risk factors such as high cholesterol, diabetes, alcohol and hypertension. Furthermore, adults do not suffer the congenital and foetal heart effects seen with HIV infection.

The published study of heart disease among HIV infected children has used a small sample size. While considering the paucity of similar data regarding HIV infected children in the Indian sub continent, the present study was undertaken to determine the incidence and nature of clinical and sub clinical cardiac abnormalities in HIV infected children

AIM OF THE STUDY

To determine:

- the prevalence of cardiac dysfunction among CLHA in the age group of 2-12 years in an urban referral centre the clinical and immunological profile of the CLHA and their association with cardiac dysfunction

- the spectrum of cardiac abnormalities using electrocardiography and echocardiography

- and the utility of the symptomatology and investigations in predicting cardiac dysfunction.

SUBJECTS AND METHODS

Methodology

Study design: Descriptive study

Study place: ART centre, ICH & HC

IP wards, ICH & HC

Cardiology department, ICH & HC

Study period: Jan. 2007 to June 2008

Inclusion criteria:

Children living with HIV/AIDS between the age group 2-12 years attending ICH & HC.

Exclusion criteria:

Children with previously known acquired heart disease.

Manoeuvre

The study population comprised of 102 CLHA.One child who had previously known rheumatic heart disease was excluded from the study. Informed verbal consent was obtained from the parents or guardian for participation in the study. All children were examined according to the protocol mentioned in the proforma (annexure 1). Their

anthropometric measurements were taken. Their haemoglobin status was determined by calorimetric method at the pathology lab,ICH. The CD-4 cell counts were done by flow cytometry at HIV wing microbiology department, Madras Medical College.

All the CLHA were subjected to cardiac studies. Chest radiography was taken. Electrocardiographic studies were done with 12 lead standard ECG in NIKHON KOHDEN Cardiofax 8820K machine.

Echocardiography was done by the cardiologist using the Philips En Visor C HD Echo machine in 2-dimensional M-mode with Doppler and colour flow studies following the criteria of the American Society of Echocardiography. [59, 60, 64-65] The transducer frequencies used were 3.5, 5, 7.5Hz depending on the need. The parasternal, apical, sub-xiphoid, and the supra sterna views were used to define the intracardiac measurements and indices of cardiac function. The parasternal and apical views were obtained with the patient in the left lateral or supine position depending on what gives the best view. The parasternal long views with M mode were used for measuring the cardiac dimensions in diastole and systole. The ventricular ejection fraction and fractional shortening was automatically computed by the Echo machine by Teichole method. TR and PR gradients were estimated with doppler for assessment of pulmonary artery pressures.

Diagnostic definitions

Children who tested positive twice with rapid antigen test for HIV at ART

CENTRE, ICH were taken as HIV infected children.

HIV infection was considered to be vertically transmitted if the mother was HIV positive or had died of AIDS and there was no history of sexual abuse of the child before enrolment.

Children were classified under four clinical stages based on the WHO Revised clinical staging for HIV/AIDS children in whom diagnosis of HIV infection was confirmed.[60] (Annexure 2).

CLHA who reported cardiac symptoms such as cyanosis, dyspnoea, fatigue, palpitations, chest pain ,syncope or oedema or on examination had evidence of tachycardia, tachypnoea, increased jugular venous pressure, clubbing, cyanosis, shift of the apical impulse from the normal position for age, murmur or gallop were categorised as cardio symptomatic.

CLHA whose weight was below the third percentile for their age and sex according to WHO growth charts [61] were taken as undernourished.

CLHA with haemoglobin >11gms% were considered as not anaemic; between 7-10gms% as moderately anaemic and <7gms% as severely anaemic.[62]

The immune status of the CLHA was classified based on CD4 cell counts following the CDC Revised paediatric HIV classification based on the CD4 cell count.

(Annexure 3)[25]

Cardio thoracic ratio more than 0.5 in chest Xray was taken as cardiomegaly.

ECG and ECHO studies were interpreted by the cardiologists as per standard guidelines of the American heart association.[59, 60,64-65]

The following measurements were directly obtained and analysed: diameter of right ventricle in diastole and systole, diastolic and systolic dimensions of left ventricle, thickness of the posterior wall of left ventricle and interventricular septum during diastole.

Ventricular dilatation and hypertrophy

In assessing the reference echocardiogram measurements, the indicator used was body surface area (BSA). The Z score was calculated with base on the mean of expected measurements in normal children (normogram)[64-66] with the same BSA divided by a standard deviation. Therefore Z-score of zero represents the adjusted normal mean value and the upper and lower limits considered were +2 and -2.The ventricular dimensions above the upper limit were taken as LV and RV dilatation.

Ventricular systolic dysfunction

1. LV systolic dysfunction was defined as ejection fraction <54% and fractional shortening <28%[59] The severity of dysfunction was quantified based on FS and EF.[1, 4]

Dysfunction	**Ejection fraction %**	**Fractional shortening %**
Mild	35-53	25-27
Moderate	20-35	19-24
Severe	<20	<19

Dilated cardiomyopathy was defined as left ventricular dysfunction characterised by a diffuse decrease in myocardial contractility, with ejection fraction and

fractional shortening below normal limits (FS<28% and EF<20%) followed by left ventricular enlargement with the diastolic diameter above normal values for BSA.[59]

Pericardial effusion was diagnosed when presence of fluid was made out even in diastolic phase in the pericardial space. A small accumulation of pericardial fluid was defined as non–circumferential collection of effusion less than 10mm; moderate 10-20 mm and severe greater than 20 mm.[58]

Regurgitation through the mitral and tricuspid valves were detected by Doppler and colour flow studies and were graded as mild, moderate and severe depending on the flow into the receiving chamber.

Diastolic dysfunction was not analysed because, unlike the systolic function which can be directly arrived at, the diastolic function is complex and dependant upon number of factors such as age, preload, after load, heart rate and the coexistence of other abnormalities (e.g. MV disease). There is no good single Echo measure to arrive at diastolic function. Doppler measurements of ventricle filling pattern should not necessarily be viewed as the only reflection of ventricle diastolic function. It is a mistake to rely on single measurements such as E: A ratio or S: D ratio.[59]

Ejection fraction incorporates ventricular volume (3-dimensional parameter) and reflects global ventricular performance. Hence FS and EF were used to assess ventricle dysfunction.[59]

STATISTICAL ANALYSIS

For continuous variable mean is reported. To examine the linear trend of proportions trend chi-square was used and to find the test of association chi-square was computed. To find the measure of association between the risk factor and the outcome variable odds ratio and its 95% confidence interval was computed. The diagnostic test procedure such as sensitivity, specificity, PPV, NPV and accuracy of the tests were computed to assess the strength of the test procedure. The p value < 0.05 was considered to indicate statistical significance. All analysis were performed using SPSS (Statistical Package for Social Sciences) version 10.0.

RESULTS

Total no. of CLHA in the study = 102

Total no. of CLHA analysed in the study = 101

Total no. of CLHA excluded from the study = 1*

*(One child with the previously known acquired (rheumatic) heart disease was excluded from the study).

The results of the analysis are tabulated as follows:

Age and sex distribution of the CLHA

The average age of presentation was 6 years among the CLHA and 61.4% were male and 38.6% were female children. The difference in proportion between the male and female children across the different age groups was not statistically significant (Table: 1).

Table 1: Age and sex distribution of the CLHA.

Age group (yrs)	Male		Female		TOTAL
	n	%	n	%	
2-5	27	61.4	17	38.4	44
6-9	24	54.5	20	45.5	44
10-12	11	84.6	2	15.4	13
Total	62	61.4	39	38.6	101

($p = 0.147$; $X^2 = 0.36$)

Mode of transmission in the CLHA

Table 2: Mode of transmission in the CLHA

Transmission	N	%
Mother to child	90	89.1
Breast feeding (surrogate mother)	1	1.0
Unknown	10	9.9

Perinatal transmission was the most common mode of transmission in the CLHA. Most of the children had acquired the infection by vertical transmission (89.1%). One case had acquired it by breast feeding from a surrogate mother. Among them 21 (20.7%) children had lost their mother due to the disease and in the rest (68.3%) the mothers were positive for RVD. In the remaining 9.9% the route of transmission could not be ascertained (Table 2).

Clinical manifestations in the CLHA

The common clinical manifestations in the CLHA were hepatosplenomegaly (46.6%), followed by lymphadenopathy (18.8%) and oral candidiasis (15.8%). Encephalopathy was present in 9(8.9%) cases Tuberculosis was present in 14 cases (13.8%), chronic diarrhoea was present in 11.8%, pneumonia excluding tuberculosis was present in 8.9% and upper respiratory tract infections including CSOM and rhinitis was

present in 6%.(Fig.1).

Among them 13 children were classified under WHO clinical stage 1 (12.9%). The stage 2 and the stage 3 had an equal number of 24 cases each (23.8%). Rest of them presented in the advanced clinical stage (stage 4) of the disease (39.6%) (Fig: 2).

Nutritional status of the CLHA:

The average weight of the CLHA was 14 kgs and the mean haemoglobin was 9.3gms% .The study population comprised of 71 (70%) undernourished children. Among them 10(9.9%) of them had severe anaemia (<7gms %) and 51(50.5%) of them had moderate anaemia (7-10gms %)(Fig: 3).

Duration of illness and therapy of the CLHA at the time of cardiac evaluation:

The cardiac evaluation was done after six months from identification of the retroviral disease in 32 (31.7%) children; between one to six months in 21 (20.8%) children and less than one month duration in 48(47.5%) children.

The CLHA who were on anti-retroviral therapy were 17.8% and 82.2% of children were not on antiretroviral therapy.

Categorisation of immune status based on CD-4 cell counts

The mean of their CD-4 cell counts at the time of cardiac evaluation was 567 cells/mm^3. Of the 101 children, 30% had severe suppression of their CD-4 cell counts; 37% children had moderate suppression and 33% had no suppression of their CD-4 cell counts

(Fig: 4).

Analysis of cardiac symptomatology of the study group

On examination 44/101 (43.5%) CLHA had no symptoms and signs pertaining to the cardiovascular system. Among the CLHA, 57(56.4%) children either reported cardiac symptoms or on examination had clues to suggest cardiac dysfunction. Most common symptoms among the CLHA were dyspnoea (40.5%) and easy fatiguability (35.6%). Exertional dyspnoea was present in 23.75% of cases. Chest pain was present in 9 cases (8.9%). Palpitation was present in 10 (9.9%) CLHA. In the children who presented with oedema (10.4%), anaemia was present in 4 cases (3.9%) (Fig5).

In this study of 101 children, 46 had cardiac dysfunction (45%). Out of 46 children, four children had congestive cardiac failure and were referred for cardiac evaluation.15 cases were referred for cardiac evaluation based on clinical suspicion. Rest of the children were evaluated as a part of the study. Congestive cardiac failure was associated with the following etiologies: dilated cardiomyopathy (2/46- 4%), ventricular

septal defect (1/46- 2%) and pulmonary hypertension.

On examination tachycardia and clubbing were significantly present in those with cardiac dysfunction. Eight cases presented with a murmur on examination. Cyanosis was present in two cases (TOF/Pulmonary hypertension). Gallop was present in three cases and all of them had dilated cardiomyopathy on cardiac evaluation (Fig: 6).

Association between age groups and cardiac dysfunction

Table 3: Association between age groups and cardiac dysfunction

Age (yrs)	Cardiac dysfunction				Total n	P Value
	Present		Absent			
	n	%	n	%		
2-5	16	36.4	28	63.6	44	0.104
6-9	21	47.7	23	52.3	44	
10-12	9	69.2	4	30.8	13	
Total	46	45.5	55	54.5	101	

The prevalence of cardiac dysfunction in the first group (2-5years) was 36.4%. In the second group (6-9years) the prevalence was 47.7%. In the third group the prevalence was 69.2%. Association between a particular age group and cardiac dysfunction was not statistically significant (p=0.104). But the proportion of children with cardiac dysfunction was found to be increasing across the age groups(X^2=0.039) (Table 3).

Association between sex and cardiac dysfunction

Table 4: Association between sex and cardiac dysfunction

Sex	Cardiac dysfunction				Total	P Value
	Present		Absent			
	n	%	n	%		
Male	29	46.8	33	53.2	62	0.914
Female	17	43.6	22	56.4	39	
Total	46	45.5	55	54.5	101	

The prevalence of cardiac abnormality among the male children was 46.8% and that in female children was 43.6%. Among the CLHA who had cardiac dysfunction, male children were more common than female children, but this difference in proportion was not statistically significant (Table 4).

Association between duration of illness and cardiac dysfunction

Table 5: Association between duration of illness and cardiac dysfunction

Duration Of Illness (months)	Cardiac dysfunction				Total	P value
	Present		Absent			0.348
	n	%	n	%		
< 1	27	56.3	21	43.8	48	
1-6	4	19	17	81.0	21	
>6	15	46.9	17	53.1	32	
Total	46	45.5	55	54.5	101	

The prevalence of cardiac dysfunction in the CLHA who had their cardiac evaluation after 6 months of diagnosis of their retro viral disease was 46.9% (15 cases); between 1-6 months of diagnosis it was 19% and less than 1 month duration it was 56.3%. The difference in proportion of CLHA who had cardiac dysfunction at different times of the course of the disease was not statistically significant (Table 5).

Association between WHO clinical staging for Retroviral disease and cardiac dysfunction

Table 6: Association between WHO clinical staging for Retroviral disease and cardiac dysfunction

Clinical stages	Cardiac dysfunction				Total	P value
	Present		Absent			0.000
	n	%	n	%		
1	1	7.7	12	92.3	13	
2	5	20.8	19	79.2	24	
3	14	58.3	10	41.7	24	
4	26	65.0	14	35.0	40	

The prevalence of cardiac dysfunction in the CLHA under clinical stage I was 7.7%, in stage II was 20.8%, stage III was 58.3% and in stage IV was 65%. The proportion of children with cardiac dysfunction was found to be significantly higher in stage IV compared to other stages ($p<0.05$). The proportion was increasing as the stages were advancing ($x^{2=}$ 0.000) (Table 6).

Association between cardiac symptomatology and cardiac dysfunction

Table 7: Association between cardiac symptomatology and cardiac dysfunction

Cardiac examination	Cardiac dysfunction				Total	P value
	Present		Absent			0.535
	n	%	n	%		
Symptomatic	28	49.2	29	50.8	57	
Asymptomatic	18	40.9	26	59.1	44	
Total	46	45.5	55	54.5	101	

Sensitivity=60.8%; Specificity=47.2%; PPV=49.1%; NPV=59%; Accuracy=53.4%

Among the CLHA who had cardiac dysfunction, the difference in proportion between cardio symptomatics and asymptomatics was not statistically significant. (p value > 0.05).

Among the 46, CLHA who had cardiac dysfunction, 28 children had cardiac symptoms (Sensitivity=60.8%).

Among the 55, CLHA who had normal cardiac function, 26 children had no cardiac symptoms (specificity = 47.2%).

Of the 57 children who had symptoms/signs pertaining to cardiovascular system, 28 children showed cardiac dysfunction on echocardiography. (PPV=63%). Of the 44 children who had no cardiac symptoms and signs, 26 children showed normal cardiac functional status (NPV=68%). The over all accuracy of the symptomatology to predict

cardiac dysfunction is only 53.4%.

In the study, 18 children who had no cardiac symptoms and signs, had cardiac dysfunction on echocardiography. These children did not show any abnormality on X-ray or ECG (Table 7).

Association between anaemia, nutritional status, Immune status and ART and cardiac dysfunction.

Table 8: Assessment of risk factors to predict cardiac dysfunction in CLHA

Variable	Cardiac dysfunction		OR	95% CI	P value
	Present	Absent			
Anaemia Present	27	34	0.88	0.36–0.211	0.908
Absent	19	21			
Undernourishment Present	34	36	1.5	0.58- 3.87	0.483
Absent	12	19			
Immune suppression Present	31	37	1.01	0.40 – 2.52	0.841
Absent	15	18			
Antiretroviral therapy Present	8	10	0.95	0.30 – 2.94	1.000
Absent	38	45			

Among those who had cardiac dysfunction, patients who were anaemic, under nourished, immuno compromised or being treated with HAART, were more common, but the difference in proportion compared to cases in whom the above risk factors were absent was not statistically significant. Hence there was no positive correlation observed between anaemia, under nourishment, CD 4 cell counts and HAART therapy (Table 8).

Abnormalities observed on ECG in the CLHA

Table 9: ECG abnormalities in the CLHA

Electrocardiograph abnormalities	**n**	**%**
Sinus tachycardia	15	71
Right ventricular hypertrophy(RVH)	5	23
Left ventricular hypertrophy(LVH)	1	4
Right bundle branch block(RBBB)	2	9
Right atrial enlargement(RAE)	3	14
Non specific ST ,T changes	2	9

Among the ECG abnormalities, sinus tachycardia (71%) was the most common abnormality followed by right ventricular hypertrophy (23%). LVH was observed in one case with VSD. RBBB was observed in ASD and in isolation with mild LV dysfunction. Right atrial enlargement was seen in three (14%) cases; two children had pulmonary hypertension and one had DCM associated. Non specific ST segment and T wave changes were observed in 9% of cases (Table 9).

Echocardiographic abnormalities in the CLHA

Table 10: Echocardiographic abnormalities in the CLHA

Echo abnormalities	**n**	**%**
LV dilatation	43	42.6
LV dysfunction	36	35.6
LV hypertrophy	4	3.9
RV dysfunction	2	2
RV dilatation	2	2
Mitral regurgitation	2	2
Tricuspid regurgitation	6	5.9
Pericardial effusion	4	3.9
Pulmonary hypertension	4	3.9
Dilated cardiomyopathy	4	3.9
Congenital heart disease	3	3

The most common abnormality was LV dilatation (42.6%) followed by LV systolic dysfunction (35.6%). Isolated left ventricular hypertrophy was seen in 3% of the cases and 1 case presented with VSD. Valvular (tricuspid and mitral) regurgitations were seen in 7.9%. They were associated with DCM. In cardio asymptomatic CLHA, isolated LV dilatation and dysfunction was commonly observed.

Pericardial effusion was seen in 3.9%. Most of them were moderate effusions and

none had cardiac tamponade and required tapping. Two cases among them had tuberculosis.

DCM was noted in 3.9%. These patients were all seen in stage IV of the retroviral disease. They had recurrent chest infections and were highly compromised in clinical status. Among them 3 had congestive cardiac failure.

Congenital heart diseases accounted for 3% comprising of VSD, TOF and ASD. VSD was of large size and bidirectional shunt was present.

Only one case of pulmonary hypertension was associated with DCM. Two other children had pulmonary hypertension with ventricular dysfunction. One case was primary pulmonary hypertension with normal cardiac function (Table 10).

Severity of cardiac dysfunction among the CLHA

Table 11: Grading of dysfunction based on Ejection fraction

Ejection fraction	N	%
Severe (<20%)	4	3.9
Moderate (20-35%)	23	22.7
Mild (35-53%)	15	14.8
Normal (>/=54%)	59	58.4

Table 12: Grading of dysfunction based on Fractional shortening

Fractional shortening	n	%
Severe (<19%)	4	3.9
Moderate (19-24%)	29	11.8
Mild (25-27%)	12	28.7
Normal (>/=28%)	55	54.4

In 59 children there was normal ejection fraction (>54%). The four children who had DCM had severe cardiac dysfunction and both EF and FS were less than 20%. Moderate impairment was seen in 29 (28.7%) cases.

Fractional shortening was compromised in 46 children. Out of the 46 children, 4 (3.9%) had severe impairment in fractional shortening (<19%); 12 (11.8%) children had

moderate reduction. Mild impairment (25-27%) was seen in 29(28.7%) children.

Both EF and FS were reduced in 35.6% cases. Severe ventricular dysfunction was present in 4 cases. All of them had DCM and were in the stage IV of the retroviral disease. Moderate impairment of systolic dysfunction was present in 23 cases. Among these children most of them had clues to suggest cardiac dysfunction. Mild impairment was present in 15 cases. CLHA who had mild impairment of cardiac dysfunction were asymptomatic clinically. Cardiac symptoms were usually present in CLHA who had moderate impairment of cardiac function (Table 11 and 12).

Association between chest x-ray and cardiac dysfunction

Table 13: Association between chest x-ray and cardiac dysfunction

Chest X-ray	Cardiac dysfunction		Total	P value
	Present	Absent		
Abnormal	10	0	10	0.001
Normal	36	55	91	
Total	46	55	101	

Sensitivity=21.7%; Specificity=100%; PPV=100%; NPV=35.9%; Accuracy=64.3%.

Of the 46 children who had cardiac dysfunction on echo, chest radiography showed cardiomegaly in 10 cases (sensitivity-21.7%). In the 55 children who had their cardiac functional indices to be normal on echo, none showed any abnormality in cardiac size (specificity 100%). In all the cases where chest x ray was abnormal ECHO was also abnormal (PPV=100%). Among the 91 cases where the chest x ray was normal Echo was able to pick up abnormalities in 36 cases (NPV=35.9%). The overall accuracy of chest x ray in predicting cardiac dysfunction was only 64.3% (Table 13).

Association between ECG and cardiac dysfunction

Table 14: Association between ECG and cardiac dysfunction

ECG	Cardiac dysfunction		Total	P value
	Present	Absent		
Abnormal	16	5	21	0.003
Normal	30	50	80	
Total	46	55	101	

Sensitivity=34.8%; Specificity=90.9%; PPV=76.1%; NPV=62.5%; Accuracy=65.3% (p=0.003)

ECG showed abnormalities in 21 cases. Of the 46 children who had cardiac dysfunction on echo, ECG showed abnormalities in 16 cases (sensitivity=34.8%).

In 55 children who had normal cardiac function, ECG was normal in 50 cases (specificity=90.9%). Among 21 cases who showed abnormalities on ECG, Echo picked up abnormalities in 16 cases (PPV=76.1%). In 80 cases with normal ECG, Echo was also normal in 50 cases (NPV=62.5%). The overall accuracy of ECG in predicting cardiac dysfunction was 65.3% (Table 14).

Association between combination of both chest x ray and ECG and cardiac dysfunction

Table 15: Association between combination of both chest x ray and ECG and

cardiac dysfunction

Investigations	Cardiac dysfunction		Sensitivity	Specificity	P value
	Present	Absent			
Chest x ray					
Abnormal	10	0	21.7	100	0.001
Normal	36	55			
ECG					
Abnormal	16	30	34.8	90.9	0.003
Normal	5	50			
Chest x ray and ECG (-)					
Abnormal	7	0	15.2	100	0.009
Normal	39	55			

Sensitivity=15.2% specificity=100% NPV=58.5% PPV=100% Accuracy=61.3%

Among 46 CLHA who had cardiac dysfunction, 7 cases had abnormality on both ECG and chest x ray (sensitivity = 15.2%).

When the results of chest radiography and ECG were combined (when both showed abnormalities), the specificity was 100%, but the sensitivity decreased to 15.2% because in three cases where the X ray was abnormal the ECG did not show any abnormality. Among the 7 cases that showed abnormality in both investigations, cardiac dysfunction was present in all the 7 cases (Positive predictive value on combining both

was 100%). Among 94 cases who either did not show any abnormality or had discordance between each other, cardiac function was normal in 55 cases (negative predictive value was 58.5%). The overall accuracy of the combination in predicting cardiac dysfunction was 61.3% (Table 15).

DISCUSSION

Infection by the HIV is one of the major public health problems in the world, with high mortality and morbidity rates. There is a worldwide trend of increasing transmission among women at child bearing age, which leads to increased mother to child transmission and pediatric HIV cases.[4]

Highly active anti retroviral therapy has significantly changed the course of the disease with increased survival and improved quality of life for AIDS patients.[34] But ARV drugs do not eliminate the virus from the body; their use may simply postpone the development of the complications of the infection. All body systems including the cardiovascular system, may be affected by HIV infection.[34] Cardiac disease associated with HIV infection is an underestimated condition because the signs and symptoms are nonspecific and are often attributed to pulmonary pathologies by the physician and patients are not routinely evaluated by echocardiography. Several patterns of cardiovascular involvement have been reported in CLHA by various studies in other parts of the world.

Review of the Indian literature showed a paucity of similar data from the Indian subcontinent which holds a considerable number of PLHA. A single study of cardiac diseases in pediatric HIV patients had used a very small sample size (n=26).[7] Hence this study was undertaken to determine the prevalence and clinical spectrum of cardiac abnormalities among the CLHA in the age group of 2 to 12 years.

The choice of this age group (2-12 years) excludes patients with the rapidly progressive form who evolve to death within the first 2 years of life.[12,5] Therefore, the priority was to study patients with slow progression seen in the older age group (toddler, childhood, adolescents) with higher probability of cardiac involvement[12,17] and therapeutic interventions.[13]

In this study, there were 101 CLHA between 2-12 years of age. These children after clinical examination and hemoglobin and CD-4 cell count estimation were subjected to cardiac evaluation.

Most of them had acquired the infection by perinatal transmission. The mean age of the CLHA (6 years) and a large number of the CLHA in the advanced stage of the disease was similar to the previous study.[3] Many of them were undernourished. The difference in proportions between the two sexes across different age groups was not significant. In our study, CLHA had varied clinical presentations in addition to failure to thrive. The commonest were hepatosplenomegaly, lymphadenopathy and oral candidiasis similar to the previous Indian study.[7]

Among the CLHA 19 cases were referred for cardiac evaluation based on clinical suspicion. Rest of the cases were evaluated as a part of the study. After cardiac evaluation in 101 CLHA, the prevalence of cardiac abnormalities in our study was 45.5% similar to the previous studies.[3, 2, 1]

In our study there was no positive association between particular sex and the prevalence of cardiac abnormalities. This was not in accordance with the study[42] conducted earlier which showed a positive association with the male sex which could not be explained biologically.

The prevalence among different age groups was different, showing an increasing trend across the age groups in our study. This was similar to the study by Pong port et al[6] which showed no correlation between particular age group and cardiac involvement.

Among the CLHA with cardiac dysfunction most of them belonged to advanced clinical stages of the retroviral disease. In our study, the duration of illness did not have any significant association with the occurrence of cardiac abnormalities which may be due to only few cases among particular duration strata distracting the values.

The prevalence of cardiac involvement among the children who had no signs and symptoms pertaining to cardiovascular system in our study was 40.9% compared to the previous study by Ira shah et al which showed 72% prevalence among the cardio asymptomatics,[7] but this was a pilot study done in a small group of patients (n=26). Among the CLHA with cardiac dysfunction there was no significant statistical difference between the proportions of CLHA with cardiac symptoms and signs and without cardiac symptoms and signs. This emphasizes the need for all the CLHA to be screened for cardiac involvement irrespective of whether they have symptoms and signs related to cardiac dysfunction.

In our study, the CD-4 cell counts did not correlate statistically with the presence of cardiac dysfunction. This observation was similar to that of P^2C^2 study.[9] This is explained by the fact that CD-4 cell count is a correlate of the progression of the biological effects of viral infection on the immune system, but it does not indicate the magnitude of the clinical effects.

In our study the proportions of CLHA with cardiac dysfunction across the different grades of anemia were not statistically significant. There was no positive correlation between nutritional status (wasting) and cardiac dysfunction in the CLHA similar to the observation made by Lubega et al[3], Pong port et al[6] and P^2C^2 study[9]. The reason is that unlike other states of malnutrition in which LV mass falls as weight and height fall, the demands of mechanically driven LV hypertrophy take precedence over the catabolic influence of wasting in HIV patients. There appears to be a sparing effect of cardiac mass relative to skeletal muscle wasting in HIV infected children.[30] When this protective effect wears out, cardiac dysfunction ensues which is indicated by the observation that all patients with DCM were highly compromised in clinical status. They suffered from severe malnutrition recurrent respiratory tract infections and chronic anemia, an observation made by the previous study[2] and our study.

Our study did not show any statistical correlation between therapy with ARV drugs and presence of cardiac abnormalities. Domanski et al[33] reported cardio toxicity due to zidovudine among the PLHA. Lipshultz et al[32] concluded that there was no

increased cardiac abnormalities among those who were treated with zidovudine. Our study was unable to infer on this since long term follow up of patients on HARRT was not there in our study.

In our study the prevalence of cardiac abnormalities among CLHA detected by Echocardiography was 45.5%. Other studies[3,2,1,4,6] have also reported a similar range. The data published about this prevalence vary according to the methodology used, time of collection, profile of children studied and type of therapy used.[18] The spectrum of cardiac abnormalities among CLHA in our study is as follows: LV dilatation in isolation and in combination with LV dysfunction, LV hypertrophy, RV dilatation, RV dysfunction, dilated cardiomyopathy, valvular (tricuspid, mitral) regurgitation, pericardial effusion and pulmonary hypertension.

Our study observed LV dilatation as the most common abnormality with the prevalence of 42.6% which accords with the previous Indian study[7]. The prevalence of isolated LV dilatation which signifies the initial stages of cardiac dysfunction, in our study was 6.9% in contrast to reports of studies[1,4] from other parts of the world claiming 10-20%. The reason being different clinical profile of the CLHA who presented in advanced stage of the disease in our study. The prevalence of LV dysfunction in our study was 35.6% which is higher compared to that reported by the previous Indian study probably because in the previous study most of the cases were asymptomatic for cardiac illness and hence had more of LV hypertrophy, an earlier phase of cardiac

pathology rather than dysfunction[7]

Prospective studies have shown that LV dysfunction may progress to DCM. The prevalence of DCM in our study was 4%. This was similar to the study by Lubega et al (3.8%) from South Africa and much lower than that reported by Sherron et al (45%)[21] and Lipshultz et al (16%)[22] from the west. This could probably be explained by the increased life span and advanced cardiac disease accounted by early and effective therapeutic interventions in CLHA in the western world compared to the underprivileged and clinically compromised CLHA in the developing countries who succumb very early without treatment, even before HAART.

Pericardial effusion was seen in 3.9% in our study. Some studies have reported 14-16%[7,21,22] and some found no pericardial effusion even in a sample larger than our study. The prevalence of pulmonary hypertension was 3.9% in our study, similar to the study by Diogenes et al[2] (4.8%). This is lower compared to previous studies which were either follow up studies[6] or retrospective studies with small sample size[12].The abnormalities like DCM, pericardial effusion and pulmonary hypertension were observed more commonly in the advanced clinical stage of the retroviral disease in our study similar to other studies [2,3] .

The prevalence of congenital heart defects was 3% in our study. This is similar (2-3%) to the previous studies[24,23,22] and higher than that found in the general population(0.8%). [25] The defects observed were ASD which was asymptomatic, VSD

which presented with congestive cardiac failure and TOF, all of them with normal cardiac function. These defects may be due to the foetal and congenital effects of HIV infection.

The prevalence of ECG abnormalities in our study was 20.7%.This is similar to the prevalence in the study by Lubega et al[3] which also used standard 12 lead standard ECG and lower than Issenberg et al[31,10] (55%) and Lipshultz et al[22] (93%) who have used 24 hour ambulatory ECG in addition to standard 12 lead ECG.

The spectrum of abnormalities observed in ECG were sinus tachycardia, right ventricular hypertrophy, right bundle branch block, left ventricular hypertrophy, right atrial enlargement, non specific ST and T wave changes. Sinus tachycardia was the most common abnormality similar to the previous study.[3]

In our cardiac evaluation, Chest X ray was abnormal showing cardiomegaly only in 9.9% of cases. When the chest X ray was abnormal there was definitely an abnormality picked by ECHO. Hence the specificity was high (100%). In the chest x-ray often there was no cardiomegaly despite ECHO proven disease similar to the previous study.[22] In 36 cases it failed to detect the cardiac abnormalities. The sensitivity was low (21.7%). The chest X ray was positive in advanced lesions and negative in the early stages of cardiac involvement. Therefore the role of chest X ray as a screening tool among the CLHA to detect the early cardiac involvement was limited.

Though ECG revealed some clinically in apparent disease, the sensitivity was only 34.8% (more compared to chest X ray) and specificity was 90.9% (less than chest x ray). Its accuracy to predict cardiac involvement was only 65.3%. It failed to pick up the early stage of LV dysfunction which was sub clinical.

ECHO picked up abnormalities in 45.5% cases. It was able to detect the early changes like LV dilatation, LV systolic dysfunction, LV hypertrophy in addition to the advanced stages of involvement like DCM, pericardial effusion, pulmonary hypertension and valvular regurgitations and congenital defects. It was able to detect cardiac abnormalities even in patients who had no symptoms and signs pertaining to the cardiovascular system. Therefore ECHO was the only non invasive investigatory modality to detect cardiac involvement in the early stage for early therapeutic intervention.

Both ECG and X-ray chest proved to be poor screening tools for cardiac disease among the CLHA and ECHO serves as the single most useful, noninvasive diagnostic test to detect cardiac dysfunction in CLHA even in early stages.

Thus it is emphasized that all the CLHA have to be evaluated for cardiac disease with Echocardiography irrespective of whether they have symptoms and signs related to cardiac dysfunction.

SUMMARY

To summarise the results of the study,

- The prevalence of cardiac dysfunction among the CLHA was 45.5%. The prevalence was more among those who presented in the advanced clinical stages of the retroviral disease. The prevalence was found to be increasing across the age groups.

- The prevalence of cardiac dysfunction did not correlate with sex, nutritional status, haemoglobin levels and CD-4 cell counts.

- Among those who had cardiac dysfunction there was no significant difference in proportions between those who had symptoms and signs pertaining to cardiac dysfunction and those who did not have the symptoms and signs. This emphasizes the need for all the CLHA to be screened for cardiac involvement irrespective of whether they have symptoms and signs related to cardiac dysfunction.

- The spectrum of cardiac abnormalities observed on ECHO were LV dilatation, LV dysfunction, LV hypertrophy, DCM, RV dilatation, RV dysfunction, tricuspid and mitral regurgitation, pericardial effusion, pulmonary hypertension and congenital cardiac defects (ASD,VSD,TOF). The most common of them was LV dilatation (42.6%) followed by LV dysfunction (35.6%).

- The electrocardiography showed abnormalities in 20.6% cases. The spectrum of abnormalities observed in ECG were sinus tachycardia (commonest change), RVH, RBBB, RAE, LVH and non-specific ST and T wave changes.

- Chest x ray had high specificity but a low sensitivity.

- ECG had better sensitivity than chest x ray, but was able to detect abnormality only in 16 cases with cardiac dysfunction.

- Chest x-ray and ECG failed to pick up the abnormalities in the early stages of cardiac dysfunction.

- Echocardiography was able to detect abnormalities even in the early stages of the dysfunction when the abnormality was subtle and sub clinical. Hence ECHO serves as the single most useful non-invasive diagnostic test to detect cardiac dysfunction.

Hence, chest x-ray and ECG were poor screening tools to detect the abnormalities making ECHO the only non invasive investigation to detect the dysfunction for early cardiac intervention.

All the CLHA have to be evaluated for cardiac involvement irrespective of whether they have symptoms and signs related to cardiac dysfunction with the echocardiogram.

CONCLUSION

It was observed that the prevalence of cardiac dysfunction among the CLHA was significant (45.5%).

Chest X ray and ECG were poor screening tools to detect early cardiac involvement.

Echocardiogram is found to be a promising investigatory modality to detect early, subtle, sub clinical and progressive cardiac abnormalities.

Therefore it is suggested that all the CLHA undergo echocardiography as an important investigation irrespective of whether they are symptomatic or asymptomatic with reference to cardiac dysfunction and periodic screening thereafter.

BIBLIOGRAPHY

1. Maria do Carno Soares, Alves Cunha, Aristarco Goncalves de Siqueria, Filho, Thalita Fernandes de, Abrue, Richardo. AIDS in childhood: Cardiac involvement with and without Triple combination anti retroviral therapy. Arq Bras Cardiol 2008; 90(1):11-17.

2. Diogenes MS, Succi RC, Machado DM, Moises VA, Novo NF, Carvalho AC. Cardiac longitudinal study of children perinatally exposed to HIV typeI. Arq Bras Cardiol 2005 oct; 85(4):233-40.

3. S.Lubega, G.W. Zirembuzi, P.Lwabi. Heart diseases among children with HIV/AIDS attending pediatric infectious disease clinic at Mulago Hospital. African Health Sciences Vol 5 No 3 September 2005.

4. Thomas J. Starc, Steven E, Lipshultz, Samuel Kaplan, Kirk A. Easley, J. Timothy Bricker. Cardiac complications in Children with HIV infection. Pediatrics; 104: 2, August 1999.

5. Luginbuhl LM, Orav EJ, McIntosh K, Steven E. Lipshultz. Cardiac morbidity and related mortality in children with symptomatic HIV infection. JAMA 1993; 269:2869-2875.

6. Pong port Y ,Sittiwangakul R, Silvilairat S, Srisanthana V. Cardiac manifestations in HIV infected Thai children. Annals of Tropical Paediatrics. 2004; 24:153-159.

7. Ira shah, S.S Prabu, Sumitra V, .H.S Shasikiran. Cardiac Dysfunction in HIV infected children: A Pilot study. Indian Paediatrics Vol 42 Feb.2005: 146-149.

8. Steven E Lipshultz, Kirk A Easley, E. Johnn Orav, Samuel Kaplan, Thomas J. Starc. Cardiac dysfunction and Mortality in HIV infected children. The Prospective P^2C^2 HIV Multicentre study. Circulation 2000; 102: 1542-1548.

9. Steven E Lipshultz, Kirk A Easley, E. Johan Orav, Samuel Kaplan, Thomas J. Starc. Left Ventricular structure and function in children infected with HIV. The

Prospective P^2C^2 HIV Multicentre study. Circulation1998; 97: 1246-1256.

10. Steven e Lipshultz, Elizabeth. Cardiovascular Manifestations in HIV Infected children Vol III (21); 335-361.

11. Melvin D Cheitlin. AIDS and the cardiovascular system. Cardiomyopathy and specific Heart muscle diseases. XI; 79;2143-2152.

12. G. Barbaro. Cardiovascular Manifestations of HIV infection. Circulation 2002; 106:1420-1425.

13. Steven E Lipshultz, E. John Orav, Stephen P. Sanders, Steven D. Colan. Immunoglobulins and Left Ventricular Structure and function in Paediatric HIV infection. Circuation 1995;92:2220-2225.

14. Richard AM. Echocardiography. In: Moss and Adams. Heart disease in infants, children, and adolescents. 5th ed. Baltimore: William & Wilkins; 1995.

15. Johann-Liang R, Cervia JS, Noel GJ. Characteristics of human Immunodeficiency Virus-infected children at the time of death: an experience in the 1990s. Pediatr Infect Dis J. 1997; 16: 1145-505.

16. Lipshultz SE, Easley KA, Orav EJ, Kaplan S, Starc TJ, Bricker JT, et al. The P^2C^2 Study Group. Reliability of central echocardiographic measurements. Circulation. 1998; 98:2525.

17. Keesler MJ, Fisher SD, Lipshultz SE. Cardiac manifestations of HIV infection in infants and children. Ann N Y Acad Sci. 2001;169-77.

18. Grenier MA, Karr SS, Rakusan TA, Martin GR. Cardiac disease in children with HIV: relationship of cardiac disease to HIV symptomatology. Pediatr AIDS HIV Infect. 1994;5:174-9.

19. Starc TJ, Lipschultz SE, Easley K, et al. Incidence of cardiac abnormalities in children with HIV infection: the prospective P^2C^2 HIV study. J Pediatr 2002; 141; 327-335.

20. Lipshultz SE, Luginbuhl LM, McIntosh K, et al. Cardiac morbidity and mortality in children with HIV infection. Circulation 1992; 86: I-362.

21. Sherron P, Pickoff AS, Ferrer PL, et al. Echocardiographic evaluation of myocardial function in pediatric AIDS patients. Am Heart J 1985; 110:710.

22. Lipshultz SE, Chanock S, Sanders SP, Colan SD, Perez-Atayde A, McIntosh K. Cardiovascular manifestations of human immunodeficiency virus infection in infants and children. Am J Cardiol 1989;63:1489-1497.

23. Bannerman C, Chitsike I. Cor pulmonale in children with HIV infection. Ann Trop Paediatr 1995; 15:129- 134.

24. Vogel RL., Alboliras E.T., McSherry G.D., et al. Congenital heart defects in children of HIV positive mothers. Circulation 1988; 78: II-17.

25. Nelson Textbook of Paediatrics 17 th edition ;254:1109-1122.

26. Petitprez et al HIV and Pulmonary hypertension and comparison with primary pulmonary hypertension Circulation 1994; 89:2722-2727.

27. Al-Attar I, Orav EJ, Exil V, McIntosh K, Lipshultz SE. Survival patterns of pediatric patients with the acquired immunodeficiency syndrome. Pediatr Res. 1995; 37:169A. Abstract.

28. Choi S, Lagakos SW, Schooley TT, Volberding PA. CD41 lymphocytes are an incomplete surrogate marker for clinical progression in persons with asymptomatic

HIV infection taking zidovudine. Ann Intern Med. 1993; 118:674–680.

29. Scientific Advisory Committee on Surrogate Markers of HIV. Consensus statement. J Acquir Immun Defic Syndr Hum Retrovirol. 1995;10 (suppl 2):S114 –S116.

30. Miller TL, Orav EJ, Colan SD, Lipshultz SE. Nutritional status and cardiac mass and function in children infected with the human immunodeficiency virus. Am J Clin Nutr. 1997; 66: 660–664.

31. Issenberg HJ, Charytan M, Rubenstein A. Cardiac involvement in children with Acquired Immune Deficiency Syndrome. Am Heart J 1985; 110: 710.

32. Lipshultz SE, Orav EJ, Sanders SP, Hale AR, McIntosh K, Colan SD. Cardiac structure and function in children with human immunodeficiency virus infection treated with zidovudine. N Engl J Med. 1992; 327: *a* Principal Investigator. 1260 – 1265.

33. Domanski MJ, Sloas MM, Follmann DA, et al. Effect of zidovudine and didanosine treatment on heart function in children infected with *human* immunodeficiency virus. J Pediatr 1995;127: 137-146.

34. Lepage P, Spira R, Kalibala S, et al. Care of HIV infected children in developing countries. Pediatr Infect Dis J 1998; 17: 581-586.

35. Herskowitz A, Sharon B, Willoughby, et al. Cardiomyopathy associated with anti retroviral therapy in patients with HIV infection. Ann Int Med 1992; 116: 311-3132.

36. S Mishra, N Wig, CM Mittal, RM Pandey, G Karthikeyan, P Arora, VK Bahl. Diastolic dysfunction in Human Immunodeficiency Virus patients in North India. Indian Heart Journal 2003;55:166-168.

37. Langston C, Cooper ER, Goldfarb J, et al. HIV-related mortality in infants and children: data from the pediatric pulmonary and cardiovascular complications of vertically transmitted HIV (P^2 C^2) Study. Pediatrics 2001; 107: 328-238.

38. Subbiah Ramasamya, Reghunath Omnathd, Andiappan Rathinavela,c, Perumal Kannane, Perundurai S. Dhandapanya, Ponnambalam Annapoorania, Pitchai Balakumarf, Manjeet Singhf, Rajagopalan Ganeshb and Govindan Sadasivam Selvam.Cardiac isoform of alpha 2 macroglobulin, an early diagnostic marker for cardiac manifestations in AIDS patient. AIDS 2006, 20:1975–1986.

39. De Castro S., Migiliau G., Silvestri A, et al. Heart involvement in AIDS: a prospective study during various stages of the disease. Eur Heart J 1992;13:1452-1459.

40. Fink L, Reichek N, Sutton MG. Cardiac abnormalities in acquired immune deficiency syndrome. Am J Cardiol 1984; 54:1161-1163.

41. Dr BD Prendergast, HIV and Cardiovascular Medicine- Prendergast 89 (7) 793 – Heart.

42. Starc TJ, Lipshultz SE, Easley KA, Kaplan S, Bricker JT, Colan SD, Lai WW, Gersony WM, Sopko G, Moodie DS, Schluchter MD. Incidence of cardiac abnormalities in children with human immunodeficiency virus infection: The prospective P2C2 HIV study. J Pediatr. 2002 Sep; 141 (3):327-34.

43. Kavanaugh-McHugh AL, Ruff AJ, Rowe S, et al. Cardiac abnormalities in a multi-center interventional study of children with symptomatic HIV infection. The ACTG 043. Pediatr Res 1991; 28: 1040.

44. UN AIDS 2008 Report on the Global AIDS epidemic – data. UN AIDS Org/Global Report/ 2008.

45. Assessment of Asymptomatic Heart Disease in Children with HIV. U. S Govt Clinical Trials Hassdah Medical Organization.

46. Magula NP, Mayosi BM. Cardiac involvement in HIV-infected people living in Africa: a review. Cardiovasc J S Afr 2003;14: 231-237.

47. Michael P. Dubé, MD, Co-Chair; Steven E. Lipshultz, MD, Co-Chair; Carl J

Fichtenbaum, MD; Richard Greenberg, MD; Alison D. Schecter, MD; Stacy D. Fisher, MD; Effects of HIV Infection and Antiretroviral Therapy on the Heart and Vasculature -Circulation. 2008;118:e 36-e40.

48. Giuseppe Barbaro. Pathogenesis of HIV- associated heart disease. AIDS 2003, 17 (suppl 1):S12–S20.

49. Lai WW, Lipshultz E et, al. Prevalence of congenital cardiovascular malformation in children of HIV infected mother: The Prospective P^2C^2 Multicentre study abstract Circulation (in press).

50. Jennifer Holmes yearly, Myocardial Macrophage Phenotypic Variation and Cytokine-Mediated Induction of HIV-Associated Cardiac Disease: Thesis for University of Massachusetts Medical School, 2008.

51. Gu J, Dische R, Anderson V, et al. Evidence of autoimmune mechanism of cardiac pathology in AIDS patients; Circulation 1992; 86:1795.

52. Dworkin BM. Selenium deficiency in AIDS. J parenteral and enteral Nutr 1999; 13: 644-647.

53. Waber LJ, Valle D, et al. Carnitine deficiency presenting as familial cardiomyopathy; a treatable defect in carnitine transport. J Pediatr 1982; 101: 700-705.

54. Parker TG, Schneider MD. Growth factors, proto oncogenes and plasticity of cardiac phenotype. Ann Rev Physiol 1991; 53: 179-200.

55. Nina Rakhlin, Priscilla Hsue, Melvin Cheitlin. HIV Insight Knowledge Base. U.S department of veteran affairs. August, 2008.

56. Carlos S. Restrepo, Lisa Diethelm, Julio A. Lemos, Enrique Vela´squez, Ty A. Ovella, MD Santiago Martinez, Jorge Carrillo, Diego F. Lemos, Cardiovascular Complications of Human Immunodeficiency Virus Infection. 2006 vol 2 ;1: 214-220.

57. Perloff. The Clinical Recognition of Congenital Heart Disease, 4th edition.

58. Feigenbaum. H. Diseases of the Myocardium. In: Echocardiography; 2004; 6th edition: 248-250.

59. Moss and Adams Heart Disease in Infants, Children, Adolescents. In: Echocardiography; 2007; 7th edition: 124-128.

60. The WHO Revised Pediatric clinical staging system. Growth charts,

61. WHO Child Growth Standards, 2007 WHO Reference.

62. WHO Guidelines on classification of Anemia in children.

63. Committee of the American Heart Associations on Electrocardiography Recommendations for standardization of electrocardiographic leads and interpretation of electrocardiography.

64. WL Henry, JM Gardin and JH Ware. Echocardiographic measurements in normal subjects from infancy to childhood. Circulation 1980; 62; 1054-1061.

65. Hp Gutgesell, M Paquet, DF duff, DG Mc Namara. Evaluation of ventricular size and function by echocardiography. Results in normal children. Circulation 1977; 56; 457-462.

66. ML Epstein, SJ Goldberg, Hd Allen, L Konecke and J Wood. Great vessel, cardiac chamber and wall growth patterns in normal children. Circulation 1975; 51;1124-1129.

ANNEXURES

ANNEXURE I

Data entry form

Serial No:

Name:

Age:

Sex:

Father name:

Address:

HIV status of the parents:

Mother: Alive / Dead

Positive /Negative

Father: Alive / Dead

Positive/Negative

Probable mode of transmission:

Date of diagnosis of RVD:

Date of cardiac evaluation:

H/O Presenting complaints:

History pertaining to cardiovascular system:

Breathlessness on exertion:

Fatigue:

Chest pain:

Palpitations:

Bluish discolouration of tongue and nail beds:

Syncope:

Oedema:

Examination

General Examination

Sensorium:

Tachypnoea / Dyspnoea:

Nutritional status:

Pallor:

Clubbing:

Cyanosis:

Lymphadenopathy:

Oedema:

Jugular venous pressure:

Anthropometry

Weight:

Height:

Vitals

Temperature:

Respiratory rate:

Heart rate:

Blood pressure:

Cardiovascular system

Inspection

Position of the apical impulse :

Precordial bulge:

Visible pulsations/dilated veins:

Palpation

Apex

Parasternal heave

Palpable second heart sound

Thrills

Percussion

Heart borders

Auscultation

Heart sounds

Murmurs

Miscellaneous sounds-Ejection clicks / Opening snaps / Pericardial rub

Respiratory system

Tracheal deviation

Breath sounds

Added sounds

Abdomen

Organomegaly

Nervous system

Higher functions

Focal neurological deficit

Stage of retroviral disease:

Diagnosis:

Investigations

Hemoglobin

CD-4 cell counts

Cardiac evaluation

Chest X ray

ECG

ECHO

Ejection Fraction

Fractional shortening

Right ventricle dimension in systole

in diastole

Left ventricle dimension in systole

in diastole

Thickness of LV posterior wall in diastole

Thickness of interventricular septum in diastole

Dilated cardiomyopathy

Pericardial effusion

Septal defects

Other abnormalities

Doppler and colour flow studies

Pulmonary artery pressure

Valvular regurgitation

TR gradient

PR gradient

ANNEXURE: 2

WHO REVISED CLINICAL STAGING IN HIV/AIDS CHILDREN

Clinical stage 1:

- Asyptomatic
- Persistent generalised lymphadenopathy

Clinical stage 2 :

- Unexplained persistent hepatosplenomegaly
- Papular pruritic eruptions
- Extensive wart virus infection
- Extensive molluscum contagiosum
- Recurrent oral ulcerations
- Unexplained persistent parotid enlargement
- Linear gingival erythema
- Herpes zoster
- Recurrent or chronic respiratory tract infections (otitis media, otorrhoea, sinusitis, tonsillitis)

Fungal nail infections

Clinical stage 3:

- Moderate unexplained malnutrition not adequately responding to standard therapy
- Unexplained persistent diarrhoea(14 days or more)
- Unexplained persistent fever (above 37.5 intermittent or constant ,for longer than 1 month)
- Persistent oral candida(outside first 6 to 8 weeks of life)
- Oral hairy leukoplakia
- Acute necrotising ulcerative gingivitis/peri odontitis/TB lymphadenitis
- Pulmonary TB
- Severe recurrent persumed bacterial pneumonia

    Symptomatic lymphoid interstitial pneumonitis

    Chronic HIV associated lung disease including bronchiectasis
- Unexplained anaemia (less than 8 gm%),neutropenia(less than 500/c.mm) or chronic thrombocytopenia (less than 50000/c.mm)
- HIV associated cardiomyopathy or HIV associated nephropathy

Clinical stage 4:

- Unexplained severe wasting,stunting or severe malnutrition not responding to standard therapy
- Pneumocystis pneumonia
- Recurrent severe presumed bacterial infactions (e.g.empyema, polymyositis, bone or joint infection, meningitis but excluding pneumonia)

- Chronic herpes simplex infection (orolabial or cutaneous of more than 1 month duration or visceral at any site)
- Extrapulmonary TB
- Kaposi sarcoma
- Oesophageal candidiasis (or candida of trachea, bronchi or lungs)
- CNS toxoplasmosis (outside the neonatal period)
    - HIV encephalopathy
- CMV infection; retinitis, or CMV infection affecting another organ with onset, at age over 1 month
- Extra pulmonary cryptococosis including meningitis
- Disseminated endemic mycosis (extra pulmonary histoplasmosis, coccidiomycosis, penniciollosis)
- Chronic cryptosporidiosis
- Chronic isosporiosis
- Disseminated non tuberculus mycobacterail infection
- Cerebral or B cell non hodgkins lymphoma
- Acquired HIV associated rectal fistula
- Progressive multifocal leucoencephalopathy

ANNEXURE : 3

PEDIATRIC IMMUNOLOGICAL CLASSIFICATION (CDC)

Immune category	< 12 months		1–5 years		6 –12 years	
	No./mm3	**%**	**No./ mm3**	**%**	**No./ mm3**	**%**
Category 1: No suppression	≥ 1500	≥ 25%	≥ 1000	≥ 25%	≥ 500	≥ 25%
Category 2: Moderate	750–1499	15%–24%	500–999	15%–24%	200–499	15%–24%
Category 3: Severe	<750	<15%	<500	<15%	<200	<15%

ABBREVIATIONS

ARV- Anti Retro Viral

PLHA- Person Living with HIV/AIDS

CLHA- Children Living with HIV/AIDS

HIV-Human Immunodeficiency Virus

AIDS-Acquired Immuno Deficiency Syndrome

CD- Cluster Differentiation

TNF- Tumor Necrosis Factor

TGF- Tumor Growth Factor

ffPCR- Polymerase Chain Reaction

DCM- Dilated Cardio Myopathy

IL- Inter Leukin

RV- Right Ventricle

LV- Left Ventricle

HAART- Highly Active Anti Retroviral Therapy

ECG-Electro Cardio Graph

ECHO- Echocardiography

Ig- Immunoglobulin

EF- Ejection Fraction

FS-Fractional Shortening

TR –Tricuspid regurgitation , PR- Pulmonary regurgitation

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Certificate

The dissertation committee for 2005, Institute of Child health and Hospital for Children, Madras Medical College, Chennai comprising of the following members has granted permission to MD postgraduate Dr.M.Anitha to proceed with her study titled **"Incidence of cardiac dysfunction in HIV infected children in age group 2-12 years in an urban referral centre"** after carefully scrutinizing her study proposal with special reference to ethical standards, methodology and relevance. Her study proposal was approved on 05.10.2005.

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